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UNIVERSITY OF NORTHERN COLORADO

Greeley, Colorado

The Graduate School

VALIDATION OF THE SIX-MINUTE WALK TEST FOR  
PREDICTING PEAK OXYGEN CONSUMPTION  
IN CANCER SURVIVORS

A Thesis Submitted in Partial Fulfillment  
of the Requirements for the Degree of  
Master of Science

Alexandra Nicole Schumacher

College of Natural and Health Sciences  
School of Sport and Exercise Science  
Exercise Physiology

May 2017

This Thesis by: Alexandra Nicole Schumacher

Entitled: *Validation of the Six-Minute Walk Test for Predicting Peak Oxygen Consumption in Cancer Survivors*

has been approved as meeting the requirement for the Degree of Master of Science in the College of Natural and Health Science in the School of Sport and Exercise Science, Program of Exercise Science Program

Accepted by the Thesis Committee:

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Accepted by the Graduate School

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## ABSTRACT

Schumacher, Alexandra Nicole. *Validation of the Six-Minute Walk Test for Predicting Peak Oxygen Consumption in Cancer Survivors*. Unpublished Master of Science Thesis, University of Northern Colorado, 2017.

Exercise improves cardiovascular function in cancer survivors (CS) suffering from treatment-related toxicities, such as decreased peak oxygen consumption ( $VO_{2peak}$ ). Establishing valid assessment protocols that determine  $VO_{2peak}$  are essential for developing individualized exercise prescriptions for cancer rehabilitation programs. The University of Northern Colorado Cancer Rehabilitation Institute (UNCCRI) has developed a valid cancer-specific  $VO_{2peak}$  treadmill protocol to address this need. The six-minute walk test (6MWT) is an exercise assessment used in many populations with chronic disease to predict  $VO_{2peak}$  but it is not clear whether this test accurately assesses  $VO_{2peak}$  in CS. The 6MWT is simple, inexpensive, and representative of daily living activities. **Purpose:** To assess the validity of predicted  $VO_{2peak}$  from the 6MWT compared to the UNCCRI treadmill protocol in CS. **Methods:** 128 CS completed a UNCCRI treadmill protocol and a 6MWT one week apart in randomized order to obtain  $VO_{2peak}$  (mL/kg/min).  $VO_{2peak}$  values from the UNCCRI treadmill protocol were compared against four common 6MWT  $VO_{2peak}$  prediction equations. **Results:** All four 6MWT prediction equations significantly ( $p < 0.001$ ) underestimated  $VO_{2peak}$  with predicted values ranging from  $8.3 \pm 3.8$  to  $18.9 \pm 3.0$  mL/kg/min, while the UNCCRI treadmill protocol yielded a much higher value of  $24.7 \pm 7.4$ . A positive strong

correlation occurred between the UNCCRI treadmill protocol and one of the 6MWT prediction equations ( $r = 0.83$ ) and a moderately strong correlation occurred between the UNCCRI treadmill protocol and another 6MWT equation ( $r = 0.70$ ). Maximum heart rates were significantly higher ( $p < 0.001$ ) during the UNCCRI treadmill protocol compared to the 6MWT ( $150 \pm 21$  bpm vs.  $109 \pm 21$  bpm). Conclusion: These findings suggest that the 6MWT is not a valid test for predicting  $\text{VO}_{2\text{peak}}$  in CS due to its underestimation when using all four equations. The UNCCRI treadmill protocol is a more accurate means of assessing  $\text{VO}_{2\text{peak}}$  in CS in order to correctly prescribe an individualized exercise rehabilitation program.

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*In life, it's not where you go – it's who you travel with. -Charles M. Schulz*

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## **CHAPTER I**

### **INTRODUCTION**

The number of people living beyond a cancer diagnosis in the United States is expected to rise to almost 19 million by 2024 (National Cancer Institute [NCI], 2016). Although cancer accounts for nearly one in four deaths, death rates are continuing to decline (NCI, 2016). Due to an increase in the number of cancer survivors (CS), cancer is being viewed as a chronic illness requiring long term management and rehabilitation (Spence, Heesch, & Brown, 2010). Cancer and its treatment can result in significant toxic side effects that impact the cardiopulmonary system. Cardiotoxicity from chemotherapy leads to decreases in cardiac output and aerobic capacity, resulting in complications such as cardiomyopathy and left ventricular dysfunction (Carver et al., 2007; Dy & Adjei, 2013; Eschenhagen et al., 2011; Yusuf, Razeghi, & Yeh, 2008). Treatment toxicities can be amplified in elderly CS because gerontological populations are more inclined to have increased rates of heart failure, coronary artery disease, arrhythmias, and left ventricular dysfunction (Sawhney, Sehl, & Naeim, 2005). Many cancer rehabilitation programs exist to combat the physiological deficits from treatment through exercise interventions and are primarily focused on improving quality of life.

Exercise interventions are feasible in CS and a prescriptive plan leads to physiological improvement in areas such as muscular strength and aerobic capacity (Spence et al., 2010). Peak oxygen uptake ( $VO_{2peak}$ ) is a measure of aerobic fitness that is consistently lower in CS compared to age-matched healthy individuals, and is often directly affected by the cytotoxic therapies that adversely impact the organ systems involved in exercise (Jones et al., 2011). Exercise rehabilitation in CS has a positive impact on cardiorespiratory function and consequently increases  $VO_{2peak}$ . The results of a  $VO_{2peak}$  assessment can provide clinicians with baseline information needed to prescribe the correct intensity of exercise as well as the correct progression throughout a cancer rehabilitation program. Establishing valid assessment protocols that determine  $VO_{2peak}$  are essential for developing individualized exercise prescriptions for cancer rehabilitation programs.

Maximal cardiopulmonary exercise testing (CPET) is considered the gold standard for measuring  $VO_{2peak}$ , but it can be expensive, time consuming, and requires trained medical personnel to be present. CPET has been found to be safe and feasible for those with advanced cancer (Jones et al., 2007) but some CPET protocols may be too difficult for CS to complete while others provide inaccurate results (Shackelford, Brown, Peterson, Schaffer, & Hayward, 2015). The University of Northern Colorado Cancer Rehabilitation Institute (UNCCRI) developed an accurate and valid treadmill protocol to estimate  $VO_{2peak}$  specifically for the cancer population. The UNCCRI treadmill protocol has decreased grades and speeds to accommodate virtually any pulmonary, musculoskeletal, and cardiovascular dysfunctions caused by cancer treatments (Shackelford et al., 2015). The UNCCRI treadmill protocol has more manageable

increases in intensity and provides a useful  $\text{VO}_{2\text{peak}}$  value that allows for a complete and accurate exercise prescription (Shackelford et al., 2015).

The six-minute walk test (6MWT) is a submaximal exercise assessment used in many populations with chronic disease to predict  $\text{VO}_{2\text{peak}}$  (American Thoracic Society, 2002; Cahalin, Mathier, Semigran, Dec, & DiSalvo, 1996; Ross, Murthy, Wollak, & Jackson, 2010; Zugck et al., 2000), but it is not clear whether this test accurately assesses  $\text{VO}_{2\text{peak}}$  in CS. The 6MWT is favored in clinical populations because it is simple, inexpensive, and representative of activities of daily living.

### **Statement of Purpose**

The purpose of this study is to evaluate the validity of the 6MWT for predicting  $\text{VO}_{2\text{peak}}$  compared to the UNCCRI treadmill protocol in CS.

### **Research Hypotheses**

- H1     The  $\text{VO}_{2\text{peak}}$  predicted from the 6MWT equations will be significantly lower than the  $\text{VO}_{2\text{peak}}$  obtained from the UNCCRI treadmill protocol.
- H2     The predicted  $\text{VO}_{2\text{peak}}$  from the multivariate 6MWT equations will have a higher correlation with the UNCCRI treadmill protocol  $\text{VO}_{2\text{peak}}$ .

## **CHAPTER II**

### **REVIEW OF LITERATURE**

#### **Introduction**

Cancer is a disease characterized by abnormal cell growth and division. There are over a hundred different types of cancer, the most common being breast, lung and bronchus, prostate, and colorectal (NCI, 2016). Over 1.6 million new cases of cancer were predicted to be diagnosed in 2016 within the United States (ACS, 2016). In the U.S., the lifetime risk of developing cancer is 42% for men and 38% for women (ACS, 2016). Even though death rates for the most common cancers are declining, cancer is the leading cause of death worldwide and accounts for nearly 1 of every 4 deaths (NCI, 2016). The number of people living beyond a cancer diagnosis in the U.S. is suspected to rise to almost 19 million by 2024 compared to 14.5 million in 2014 (NCI, 2016). As the number of cancer survivors (CS) continues to increase, it is imperative that cancer rehabilitation programs utilize proper assessment and training techniques. Exercise opposes the physiological decline in CS and an individual exercise prescription formulated from an initial assessment can help improve quality of life after a cancer diagnoses.



### **Cardiopulmonary Toxicity in Cancer Survivors**

Cancer and its therapies for cancer can result in detrimental side effects that may significantly impact the cardiopulmonary system. The most common cancer treatments include surgery, chemotherapy, and radiation therapy. Chemotherapy drugs are especially known for eliciting severe toxic effects to the different physiological systems. Anthracyclines are one common class of chemotherapy agents that result in direct DNA damage through intercalation, interference with DNA repair through the inhibition of topoisomerase II, and the formation of free radicals. This damage and disruption leads to the eventual apoptosis of cells (Arola et al., 2000; Monsuez, Charniot, Vignat, & Artigou, 2010). Radiation therapy leads to similar DNA damage and cell death. Unfortunately, these treatments do not specifically target cancer cells and are concurrently toxic to healthy tissues resulting in detrimental symptoms (Eschenhagen et al., 2011).

The toxic effects of chemotherapy have been extensively studied in relation to cardiac function. Common cardiotoxicities of chemotherapy include arrhythmias, left ventricular dysfunction, myocardial ischemia, and cardiomyopathy with or without congestive heart failure (Carver et al., 2007; Dy & Adjei, 2013; Eschenhagen et al., 2011; Yusuf et al., 2008). Cardiac damage from radiation therapy can lead to coronary artery disease (CAD), valve diseases, chronic pericardial disease, arrhythmias, conduction disturbances, cardiomyopathy, and carotid artery stenosis (Carver et al., 2007; DeSantis et al., 2014). Thoracic radiotherapy can also damage the vascular network, resulting in reduced capillarization, decreased blood perfusion, anemia, and interstitial edema (Schneider, Dennehy, & Carter, 2003). Deficiencies within the cardiovascular system of

supplying oxygen and nutrients to the major organ systems of the body can significantly reduce CS quality of daily living.

The pulmonary system is a key component in healthy cardiorespiratory function. Radiotherapy to the chest often results in radiation pneumonitis, pulmonary fibrosis, and decreased pulmonary function (Carver et al., 2007). These toxicities result in decreases in total and vital lung capacity, compromising the efficiency of oxygen diffusion and carbon dioxide removal (Schneider, Hsieh, Sprod, Carter, & Hayward, 2007). Adverse effects from chemotherapy include interstitial injury with the impairment of alveolar capillary membranes (Marulli et al., 2010). The incidence of radiation pneumonitis has been found to be five times greater with the addition of chemotherapy (Parashar et al., 2011). Palma et al. (2012) found that of those undergoing concurrent chemotherapy for non-small cell lung cancer (NSCLC), 30% are symptomatic of pneumonitis, increasing the rate of oxygen dependence. The highest risk of radiation pneumonitis (>50%) occurs in CS greater than 65 years due to the likelihood of comorbid conditions (Palma et al., 2012; Parashar et al., 2011). A decrease in pulmonary reserve from these treatments may prevent patients from undergoing potential curative surgery to remove cancer (Sawhney et al., 2005). Surgery for tumor removal in the lungs can also impact lung function adversely due to an increase in scar tissue (DeSantis et al., 2014).

### **Guidelines for Physical Activity in Cancer Survivors**

Physical activity improves physiological functioning in healthy individuals and those managing chronic disease conditions (Stevinson, Lawlor, & Fox, 2004). Physical activity of any kind can result in higher physical functioning, but an exercise prescription including 20-30 min of moderate intensity activity most days of the week was found to

have the greatest benefit for functional capacity in elderly (Brach, Simonsick, Kritchevsky, Yaffe, & Newman, 2004). With advancements in early detection and improved treatments, cancer is being viewed more often as a chronic illness requiring long term management and rehabilitation (Spence et al., 2010). Cancer treatments may lead to prolonged periods of inactivity which often lingers after treatment has ended (Burnham & Wilcox, 2002; Doyle et al., 2006; Midtgaard et al., 2013). In CS, physical activity not only helps to manage any co-occurring chronic conditions, but helps prevent reoccurring cancer and secondary cancers (Doyle et al., 2006). In women with breast cancer who followed the U.S. guidelines for physical activity, there was found to be a 26-40% lower risk of death from reoccurrence (Holmes, 2005). The area of physical rehabilitation utilizing an exercise prescription with aerobic and resistance components for CS is a growing field gaining plenty of momentum due to the support from research. Primary evidence from a systematic review citing 33 controlled trials concluded that physical activity through exercise interventions in CS leads to moderate increases in physical function, further resulting in increased activities of daily living (Stevinson et al., 2004). A similar systematic review of 10 studies with exercise interventions in CS concluded that exercise is feasible and provides a physiological improvement in several areas including strength and aerobic capacity during cancer rehabilitation (Spence et al., 2010). Recently, it was concluded that exercise training may help increase exercise capacity for people following lung resection in those diagnosed NSCLC (Cavalheri, Tahirah, Nonoyama, Jenkins, & Hill, 2014).

In 2010, the American College of Sports Medicine (ACSM) hosted a roundtable discussion with several professionals in the cancer rehabilitation field. They concluded

that exercise training during and after cancer treatment is safe and results in improvements in physical functioning, quality of life, and cancer related fatigue (Schmitz et al., 2010). Physical activity guidelines have been established to accommodate other chronic health conditions, and the ACSM discussion determined the current guidelines of 150 minutes per week of moderate activity or 75 minutes per week of vigorous activity, are appropriate for CS (Schmitz et al., 2010). However, it was cautioned that exercise interventions in CS should be individualized and monitored by professionals in the field due to possible differences in treatments, pre-aerobic fitness, comorbidities, responses to treatment, and any other adverse effects (Schmitz et al., 2010; Schneider et al., 2007).

### **Maximum and Peak Oxygen Consumption**

$\text{VO}_{2\text{max}}$  is an assessment of cardiorespiratory fitness (CRF) measuring the ability of the cardiorespiratory system to utilize oxygen through intake and transport to skeletal muscle for ATP synthesis. CRF is a powerful predictor of mortality in healthy populations.  $\text{VO}_{2\text{max}}$  is the product of maximum cardiac output and maximum arterial-mixed venous oxygen difference, measured in absolute (L/min) or relative (mL/kg/min) terms.  $\text{VO}_{2\text{max}}$  declines with inactivity, age, and disease conditions, and is an important measure to monitor physiological status after an intervention. A meta-analysis of 4884 subjects showed that there is a decline in  $\text{VO}_{2\text{max}}$  of approximately 10 mL/kg/min per decade (Fitzgerald, Tanaka, Tran, & Seals, 1997; Lakoski, Eves, Douglas, & Jones, 2012).

A true measure of  $\text{VO}_{2\text{max}}$  requires that an individual reach a Respiratory Exchange Ratio (RER) greater than 1.15, blood lactate levels greater than 8 mmol/L, and reach a plateau in oxygen consumption during maximal exercise testing measured by gas

analysis (ACSM, 2013). When criteria are not reached, it is considered to be a measurement of peak oxygen consumption.  $\text{VO}_{2\text{peak}}$  is defined as the highest oxygen consumption measured during the last 30 seconds of a symptom limited exercise test and is likely a valid measure of  $\text{VO}_{2\text{max}}$  during maximum effort (Day, Rossiter, Coats, Skasick, & Whipp, 2003; May et al., 2010; Zugck et al., 2000).  $\text{VO}_{2\text{peak}}$  also measures the ability of the cardiorespiratory system to deliver oxygen to skeletal muscle and the efficiency of the muscle to utilize the oxygen, however it is more reproducible than  $\text{VO}_{2\text{max}}$  (Day et al., 2003). In a study of 26 control subjects and 55 subjects with CAD, 23% did not reach a plateau during  $\text{VO}_{2\text{max}}$  testing (Eldridge, Ramsey-Green, Hossack, 1986), and more recently only 17% of 71 subjects who exercised to their maximum limit of tolerance reached a plateau during testing (Day et al., 2003). Cardiac responses between subjects who did or did not reach a plateau did not differ, concluding that  $\text{VO}_{2\text{peak}}$  is a valid measure of maximum cardiac capacity (Eldridge et al., 1986).  $\text{VO}_{2\text{peak}}$  has gained acceptance as a measure of  $\text{VO}_{2\text{max}}$  in clinical populations (Cote, Pinto-Plata, Kasprzyk, Dordelly, & Celli, 2007).

$\text{VO}_{2\text{peak}}$  is the measure often used in CS to assess CRF (May et al., 2010; Schmidt, Vogt, Thiel, Jager, & Banzer, 2013) and greater CRF is associated with a reduced risk of dying from cancer (Doyle et al., 2006; Jones et al., 2011; Klika, Callahan, & Drum, 2009; Peel et al., 2009).  $\text{VO}_{2\text{peak}}$  is consistently lower in CS, often directly a result of the cytotoxic therapies that adversely impact the organ systems involved in exercise (Jones et al., 2011). Smoot, Johnson, Duda, Krasnoff, & Dodd (2012) found the mean  $\text{VO}_{2\text{peak}}$  in 120 breast CS to be 25 ml/kg/min, which falls below the 30<sup>th</sup> percentile for published healthy norms. Another study found the mean  $\text{VO}_{2\text{peak}}$  value for 346 pre-surgical patients

with NSCLC to be  $16 \pm 0.4$  mL/kg/min, equivalent to only 36% of sex and age matched individuals (Loewen et al., 2007). Burnett, Kluding, Porter, Fabian, & Klemp (2013) found that 77% of their study participants with breast cancer had a  $VO_{2max}$  below the 20<sup>th</sup> percentile for norms.

Exercise rehabilitation in CS has proven to have a positive impact on cardiorespiratory function and thus increases  $VO_{2peak}$ . A recent study found a significant improvement in  $VO_{2peak}$  of over 3 mL/kg/min after a 3-month exercise intervention (Repka et al., 2014). A meta-analysis of pooled data from six different exercise intervention studies in CS (N=571) concluded that there was a significant increase in  $VO_{2peak}$  of almost 3 mL/kg/min, compared with a decrease in  $VO_{2peak}$  of -1 mL/kg/min in those CS who didn't receive an exercise intervention (Jones et al., 2011). In a different intervention study it was concluded that physical activity was able to blunt a decline in  $VO_{2max}$  by 8% (Courneya et al., 2007), and similar results have been observed by others (Midtgaard et al., 2013; Quist et al., 2006; Schneider et al., 2007). Contrary to the previous results, 37 CS of multiple myeloma underwent a three-month exercise intervention with no significant change in oxygen consumption ( $p = 0.057$ ) (Groeneveldt et al., 2013). There was a positive improvement in  $VO_{2peak}$ , but the result was not significant. This was likely due to the intensity of the intervention being less than (50% HRR) other similar studies (Groeneveldt et al., 2013).

### **Exercise Testing in Cancer Survivors**

#### **Cardiopulmonary Exercise Testing**

Maximal cardiopulmonary exercise testing (CPET) is considered the “gold standard” for measuring  $VO_{2max}$  (Burnett et al., 2013; Turner, Eastwood, Cecins, Hillman

& Jenkins, 2004). CPET requires gas analysis with a metabolic cart, is expensive, time consuming, and requires trained medical personnel to be present, especially in clinical populations. The American Thoracic Society (ATS) defines formal CPET as a test to provide a global assessment of the exercise response and an objective determination of functional capacity or impairment. It can determine the appropriate intensity needed to perform prolonged exercise and define underlying pathophysiologic mechanisms (ATS, 2002).

During CPET testing, workload is increased progressively until symptoms force discontinuation of the test (Cote et al., 2007). CPET can be conducted using gas analysis during various treadmill, step, and cycle ergometer protocols. Validated treadmill protocols are safe, reliable, and the ACSM provides accurate prediction equations to estimate  $\text{VO}_{2\text{max}}$  clinically using the last stage of completion when gas analysis is not available (ACSM, 2013).  $\text{VO}_{2\text{max}}$  has been shown to be 5-10% higher when a treadmill protocol is used compared with a cycle ergometer test protocol (Bruce, Kusumi, & Hosmer, 1973; Cahalin et al., 1996; Jones et al., 2007).

Exercise performance can be greatly reduced in patients with heart failure and similar diseases affecting cardiopulmonary systems (Zugck et al., 2000). CPET is a powerful tool that can provide information on the nature of cardiorespiratory response to exercise in chronic disease populations (Cote et al., 2007). Ramp protocols are commonly utilized in elderly or clinical populations with more limited capacity. These protocols can be less intimidating because they increase speed and grade continuously to reach peak cardiovascular responses (Bader, Maguire, & Balady, 1999). The lower the workload increments, the less likely that tests will be terminated due to other factors

other than maximum cardiopulmonary responses, thus reducing errors of estimation for  $\text{VO}_{2\text{max}}$  (Shackelford et al., 2015). Reliable, accurate, and valid CPET are of utmost importance in clinical populations in order to optimize rehabilitation programs, prescribe individual training intensities, and to improve quality of life for patients (De Backer et al., 2007; Gayda, Temfemo, Choquet, & Ahmaidi, 2004).

Promising research has led to an increase in cancer rehabilitation programs, yet there are few standards for assessing exercise capacity in CS (Stubblefield, 2013). Clinics assessing CS may choose to use a submaximal test due to impaired balance and coordination even when CPET has been found to be safe and feasible for those with advanced cancer (Jones et al., 2007; Klika et al., 2009). Like other healthy and chronic disease populations, CPET in CS is very important for screening, exercise prescription and determination of exercise capacity (Jones et al., 2007).

The University of Northern Colorado Cancer Rehabilitation Institute (UNCCRI) has developed an accurate and valid treadmill protocol to estimate  $\text{VO}_{2\text{peak}}$  in a cancer specific population. CPET protocols for healthy or other populations may be too difficult for CS to complete safely, therefore the UNCCRI protocol has decreased grades and speeds to accommodate any pulmonary, musculoskeletal, and cardiovascular dysfunctions caused by cancer treatments (Shackelford et al., 2015). Both CS and apparently healthy subjects performed a Bruce treadmill protocol and the UNCCRI treadmill protocol with and without gas analysis. The correlation for all participants between  $\text{VO}_{2\text{peak}}$  with and without gas analysis for the UNCCRI protocol was  $r = 0.90$ . These results suggest that ACSM's walking/running equations are valid for determining  $\text{VO}_{2\text{peak}}$  in CS and gas analysis is not required with this protocol. No CS had any adverse



effects when completing any of the protocols, indicating CS can complete a  $\text{VO}_{2\text{peak}}$  test safely. In CS, heart rates during the Bruce protocol were significantly lower at termination than the UNCCRI protocol. CS often terminated the Bruce protocol due more to muscle fatigue than actual cardiorespiratory effects. The Bruce has been shown to overestimate  $\text{VO}_{2\text{peak}}$  and thus will yield inaccurate prescriptions that could hinder CS if too intense (Bader et al., 1999; Shackelford et al., 2015). The UNCCRI protocol is more appropriate due to smaller work increments, which yield a more accurate relationship between oxygen supply and demand (Jones et al., 2007; Shackelford et al., 2015). Establishing accurate  $\text{VO}_{2\text{peak}}$  values for CS is the first step in the process of designing and implementing an accurate exercise prescription.

There are several instances why maximal testing may not be performed. CPET may not be widely available to clinics outside of hospitals due to expense and the availability of medical personnel, and may be contraindicated in severely limited populations (Burnett et al., 2013; Cahalin et al., 1996; Guyatt et al., 1985). It may be perceived that CPET places an unwarranted burden on patients due to the test being exhaustive, thus bringing safety into question. In patients with chronic obstructive pulmonary disease (COPD), it was found that symptoms interfere long before a possible  $\text{VO}_{2\text{peak}}$  could be achieved (Cote et al., 2007). Studies have reported that the gas analysis apparatus may be extremely uncomfortable for patients and could yield inaccurate results (Shackelford et al, 2015; Zugck et al., 2000). CPET may also be impractical for populations who need frequent assessments (Green, Watts, Rankin, Wong, & Driscoll, 2001).

For these reasons, submaximal testing is often chosen in lieu of a maximal test in clinical environments without access to formal CPET. Submaximal testing allows for a measure of sustainable cardiovascular response to exercise capacity safely without maximizing heart rate (Burnett et al., 2013). Submaximal testing at 85% age predicted heart rate max shows a strong correlation ( $r = 0.89$ ) with predicted  $VO_{2max}$  (Burnett et al., 2013). May et al. (2010) concluded that there was not a significant difference ( $p = 0.1$ ) between  $VO_{2max}$  measured from CPET versus  $VO_{2max}$  estimated from submaximal workload and a heart rate response greater than 140 bpm could serve as an alternative to maximal testing. However, it has been demonstrated that heart rate can vary substantially during submaximal workloads and it is important to assess patients based on individual needs and capacity (De Backer et al., 2007). Therefore, CPET is still the preferred protocol for initial assessments, particularly for prescribing an accurate exercise prescription during rehabilitation. However, submaximal testing allows for more frequent assessments to monitor clinical progress.

### **The Six-Minute Walk Test**

One of the most utilized submaximal tests in clinical populations is the six-minute walk test (6MWT). The 6MWT was first developed as a twelve-minute walk test but was further adapted to six minutes for more limited pulmonary populations. It has since been used in cardiac populations and rehabilitation settings (Enright, 2003; Guyatt et al., 1985). The 6MWT is a quick, inexpensive measure of physical function. It can be performed with frail, elderly, and severely limited patients (Enright & Sherrill, 1998; Guyatt et al., 1985). It is favored in clinical populations because it is less expensive, safe, and easy to administer. A walking test is also considered to be more reflective of

daily living activities in these clinical populations. A protocol for conducting the 6MWT has been standardized by the ATS. The test has high intra class correlation values greater than 0.80 and a practice test is not needed (Sciurba et al., 2003; Steffen, Hacker, & Mollinger, 2002; Weiss, 2000; Zugck et al., 2000).

Research in chronic disease populations concludes that the walk test is a valid test for monitoring exercise capacity in those with lower  $VO_{2peak}$ . In patients with COPD, interstitial lung disease, and pulmonary hypertension,  $VO_{2peak}$  measured during the 6MWT is not significantly different than  $VO_{2peak}$  during CPET (Blanco et al., 2010; Fujino et al., 2015; Hill et al., 2012; Starobin et al., 2006; Turner et al., 2004). In elderly subjects with CAD,  $VO_{2peak}$  during the 6MWT was not significantly different than CPET  $VO_{2peak}$  ( $14.3 \pm 2.9$  vs  $13.4 \pm 2.7$  mL/kg/min) (Gayda et al., 2004). Hill et al. (2012) found no significant differences between  $VO_{2peak}$  ( $p = 0.31$ ) and peak heart rate ( $p = 0.58$ ) values when comparing the 6MWT, shuttle walk tests, and a cycle CPET in those with moderate COPD. Similar findings have been observed in those with heart failure and cardiomyopathy (Faggiano, D'Aloia, Gualeni, Brentana, & Cas, 2004; Gayda et al., 2004; Zugck et al., 2000).

Lipkin, Scriven, Crake, & Poole-Wilson (1986) were the first to demonstrate a curvilinear relationship between  $VO_{2peak}$  and distance walked during the 6MWT. The findings documented that for a  $VO_{2peak}$  over 20 mL/kg/min determined by CPET, distance walked on the test varied. Since then several studies have confirmed a moderate to high positive correlational relationship between the 6MWT distance and  $VO_{2peak}$  in clinical populations (Cahalin et al., 1996; Faggiano, D'Aloia, Gualeni, Lavatelli, & Giordano, 1997; Faggiano et al., 2004; Gayda et al., 2004; Guazzi, Dickstein, Vicenzi, &

Arena, 2009; Zugck et al., 2000). Cahalin et al. (1996) developed several prediction equations from this linear relationship with distance to predict  $\text{VO}_{2\text{peak}}$  in patients with heart failure. These prediction equations are based not only on distance, but also on multivariate factors like height and weight to help reduce the variability seen in individual subjects. Ross et al. (2010) reviewed several studies and determined a valid equation to predict  $\text{VO}_{2\text{peak}}$  from 1083 patients with diverse cardiopulmonary diagnoses. Other studies concluded similar findings to Lipkin et al. (1986) that the test becomes less sensitive with greater functional capacity (Deboeck, Muylem, Vachiere, & Naeije, 2014; Fujino et al., 2015; Jehn et al., 2009; Schmidt et al., 2013;)

Given the compromised state of CS, clinics may opt for submaximal protocols like the 6MWT. Kasymjanova et al. (2009) used the 6MWT to determine which patients might have less adverse physiological effects during chemotherapy treatment. They found that those who walked a distance greater than 400m would likely have less physiological side effects from treatment. The researchers found that after two cycles of chemotherapy, the six-minute walk distance significantly declined by more than 54m in 29% of the subjects. Over half of the patients dropped out of the study due to the consequences of chemotherapy. To our knowledge, Schmidt et al. (2013) are the only researchers to evaluate the 6MWT and its correlation with  $\text{VO}_{2\text{peak}}$  in CS. They chose a cycle CPET to determine  $\text{VO}_{2\text{peak}}$  because it was considered safer and there was no need for time consuming treadmill familiarization trials. They found the 6MWT to be reliable as an assessment tool and found a correlation between distance and  $\text{VO}_{2\text{peak}}$  to be moderate ( $r = 0.67$ ). The average distance walked was  $594 \pm 81$  m and subjects walked with an intensity averaging  $86 \pm 10\%$  of their estimated heart rate maximum. The

researchers concluded the 6MWT was a valid test for determining functional capacity, but may not be sensitive enough to detect intervention related effects in patients with early stage disease. To our knowledge no studies have considered the validity of established  $\text{VO}_{2\text{peak}}$  prediction equations in cancer survivors.

## **CHAPTER III**

### **METHODOLOGY**

#### **Subjects**

A total of 128 subjects participated in this study. All participants were cancer survivors (CS) enrolled in the University of Northern Colorado Cancer Rehabilitation Institute's (UNCCRI) program. Inclusion criteria for participants included 1) diagnosed with cancer, 2) at least 18 years of age, and 3) no history of stroke, chronic respiratory difficulties, or severe arterial hypertension (resting systolic blood pressure > 200 mmHg, resting diastolic blood pressure > 110, or both). Participants were referred to UNCCRI and their medical records were obtained from the referring oncologist or primary care physician. Participants signed an informed consent upon entering the program at UNCCRI agreeing to participate in research within the institute. From 2015-2016, participants entering the UNCCRI program enrolled in and completed this study. Existing clients already in the program were recruited via flyers within the clinic for participation. Participants may have been receiving chemotherapy (N = 21), radiation therapy (N = 3), a combination of chemotherapy and radiation (N = 8), or immunotherapy (N = 3) during participation. Prior to participation, a detailed explanation was given about the study protocols.

Exclusion criteria for participants included 1) history of congestive heart failure, 2) history of myocardial infarction, 3) chronic lung disease, 4) asthma, 5) significant ambulatory issues, 6) history of coughing up blood, 7) fainting, and 8) epilepsy.

Safety was ensured by having trained Cancer Exercise Specialists (CES) supervising each protocol. The protocols used in the study were approved by the University of Northern Colorado's Institutional Review Board (see Appendix B).

### **Experimental Design**

The purpose of this study was to assess the validity of predicted  $VO_{2peak}$  from the 6MWT compared to the validated UNCCRI treadmill protocol in CS. Participants underwent a thorough initial interview and physician clearance to assure they could complete  $VO_{2peak}$  testing. Participants who qualified for the study completed one UNCCRI treadmill protocol and one 6MWT one week apart in randomized order.

#### **University of Northern Colorado Cancer Rehabilitation Institute Treadmill Protocol**

The UNCCRI treadmill protocol appears in detail in Table 1 and in Appendix C. There are 21 total stages, each stage lasts a duration of one minute. Stage 0 starts at 1 mph and a 0% incline. Speed increased by no more than 0.5 miles per hour (mph) between stages 0-6 and an incline of 2% was not observed until stage 4. Starting after the 5<sup>th</sup> stage, speed was increased by 0.1 mph and grade increased by 1% after each completed stage.

Table 1

*The University of Northern Colorado Cancer Rehabilitation Protocol*

| Stage     | Speed  | Grade | Time  |
|-----------|--------|-------|-------|
| 0         | 1.0mph | 0%    | 1 min |
| 1         | 1.5mph | 0%    | 1 min |
| 2         | 2.0mph | 0%    | 1 min |
| 3         | 2.5mph | 0%    | 1 min |
| 4         | 2.5mph | 2%    | 1 min |
| 5         | 3.0mph | 2%    | 1 min |
| 6         | 3.3mph | 3%    | 1 min |
| 7         | 3.4mph | 4%    | 1 min |
| 8         | 3.5mph | 5%    | 1 min |
| 9         | 3.6mph | 6%    | 1 min |
| 10        | 3.7mph | 7%    | 1 min |
| 11        | 3.8mph | 8%    | 1 min |
| 12        | 3.9mph | 9%    | 1 min |
| 13        | 4.0mph | 10%   | 1 min |
| 14        | 4.1mph | 11%   | 1 min |
| 15        | 4.2mph | 12%   | 1 min |
| 16        | 4.3mph | 13%   | 1 min |
| 17        | 4.4mph | 14%   | 1 min |
| 18        | 4.5mph | 15%   | 1 min |
| 19        | 4.6mph | 16%   | 1 min |
| 20        | 4.7mph | 17%   | 1 min |
| Cool Down | **     | 0%    | ***   |



Resting blood pressure (BP), resting heart rate (HR), blood oxygen saturation (SpO<sub>2</sub>), and body weight (kg) were measured before the treadmill test. Blood pressure was measured manually by auscultation a sphygmomanometer and stethoscope, HR was determined using a Polar® Heart Rate Monitor, SpO<sub>2</sub> was measured using a Clinical Guard® pulse oximeter, and body weight was measured by the InBody 770®. Three Clinical Cancer Exercise Specialists conducted the treadmill test for safety. One CES changed the grade and/or speed every minute dependent on the stage of the protocol, as well as recorded vital information. One CES recorded BP every three minutes, while one CES stood behind the participant during the duration of the protocol for spotting and safety and to monitor any safety concerns.

Before each test participants were given the following instructions: 1) BP will be taken every three minutes by a CES, 2) another CES will be recording HR and SpO<sub>2</sub> and changing speed and/or grade every minute, 3) a pulse oximeter will be placed on your finger for the duration of the test to monitor oxygen saturation every minute, 4) a CES will also stand behind you during the duration of the test for your safety and to ensure proper placement on the treadmill belt, 5) we ask that you push yourself to maximum exertion and although you may stop at any time, we would like you to reach the point where you feel that you can't physically continue, 6) we recommend that you do not use the handrails unless you feel it is absolutely necessary, 7) you must choose to use or not use the handrails for the entire protocol, 8) after maximal exertion a cool down phase at a lower speed and grade will be initiated until vitals reach near-resting measures.

The test ended when the participant reached his or her perceived maximum exertion or could not continue further. The test concluded when the participant verbally

expressed they had reached their maximum rate of perceived exertion (RPE) using a modified Borg RPE, or when the participant physically grabbed onto the handrails to signal the end of the test. Once the participant indicated they had reached maximum effort, the cool down phase was initiated. When the participant's vitals were close to resting vitals and the participant indicated that they felt safe to get off the treadmill, the treadmill was stopped. Final vitals were recorded, including the maximum HR reached. The duration of the test until maximum exertion and the final completed stage was also recorded. HR and SpO<sub>2</sub> continued to be recorded every minute, while BP and RPE continued to be recorded every three minutes. When the participant vitals were close to resting levels and the participant indicated that they felt safe to get off the treadmill, the treadmill was stopped. Final vitals were recorded, including when the maximum HR reached. The duration of the test until maximum exertion and the final completed stage was also recorded.

The American College of Sports Medicine running and walking equations were used to calculate VO<sub>2peak</sub> from the last completed stage of the protocol. If the participant was walking at maximum exertion the following equation was used: VO<sub>2peak</sub> (mL/kg/min) = (0.1 x S) + (1.8 x S x G) + 3.5. The variable S is the speed in meters/min and G is the percentage of grade in decimal form. If the participant was running at maximum exertion the following equation was used: VO<sub>2peak</sub> = (0.2 x S) + (0.9 x S x G) + 3.5. If the participant was using the handrails during the protocol the following equation was used: VO<sub>2peak</sub> = 0.694 x [the ACSM walking/running value from above] + 3.33 (ACSM, 2013).

### **The Six Minute Walk Test Protocol**

The 6MWT protocol appears in Appendix D. The 6MWT was conducted under the guidelines of the American Thoracic Society (ATS). The 6MWT took place in a 12.6-meter-long hallway at the UNCCRI. Prior to the 6MWT, participants performed a pulmonary assessment using a MIR Spirolab III® portable desktop spirometer to assess force vital capacity (FVC) and forced expiratory capacity (FEV<sub>1</sub>) of the lungs. Two CES's supervised the test to ensure participant safety.

At the beginning of the test each participant was given the following instructions: 1) walk up and down the hallway for six minutes, reaching the colored dot at each end of the hallway, 2) try to walk as far as possible in that six-minute time frame, and 3) at any time you can stop to rest or sit in one of the chairs, but we ask that you keep walking as soon as you feel able. The participants were asked to walk alone unless gait imbalances required them to have a CES near to assist them. At every minute, participants were told the time remaining and a standard verbal encouragement such as "Great job" was given. One CES kept track of the time on a stopwatch and placed a mark on the data collection sheet every time the participant completed one length of the hallway. At the end of the test, participants were asked to stop where they were and a CES marked on the wall where they had stopped. The CES measured the partial distance the participant had covered from the end of the hall to the spot on the wall with a meter stick. This value was added to the total distance of lengths completed to ensure a precise measurement of distance covered. At the end of the test HR, BP, RPE and SpO<sub>2</sub> values were recorded immediately by a CES.

The distance and other variables were used to calculate predicted  $VO_{2peak}$  from four well established prediction equations: 1)  $VO_{2peak} = 0.03 \times \text{distance (m)} + 3.98$  (Cahalin et al., 1996), 2)  $VO_{2peak} = 0.02 \times \text{distance (m)} - 0.191 \times \text{age (yrs)} - 0.07 \times \text{weight (kg)} + 0.09 \times \text{height (cm)} + 0.26 \times (\text{RPP} \times 10^{-3}) + 2.45$  (Cahalin et al., 1996), 3)  $VO_{2peak} = 0.02 + \text{distance (m)} - 0.14 \times \text{age (yrs)} - 0.07 \times \text{weight (kg)} + 0.03 \times \text{height (cm)} + 0.23 \times (\text{RPP} \times 10^{-3}) + 0.10 \times \text{FEV}_1(\text{L}) - 1.19 \times \text{FVC (L)} + 7.77$  (Cahalin et al., 1996), and 4)  $VO_{2peak} = 4.948 + 0.023 \times \text{distance (m)}$  (Ross et al., 2010).

### Statistical Analysis

A power analysis was ran using the statistical program G-power (Version 3.1) prior to the study to determine the appropriate sample size for significance. For both protocols a repeated measures ANOVA was utilized to examine the differences in  $VO_{2peak}$  obtained by the UNCCRI treadmill protocol to against  $VO_{2peak}$  values determined by the four 6MWT prediction equations. It was assumed that 1) the dependent variable of  $VO_{2peak}$  was continuous, 2) the tests were matched pairs, 3) there were no significant outliers, and 4) there was a normal distribution. Paired t-tests were utilized to test the differences between HR and SBP between the UNCCRI protocol and the 6MWT protocol. A Pearson r-correlation between the UNCCRI treadmill and 6MWT equations 1-4 to determine the strength of the relationship in  $VO_{2peak}$ . Significance was set to  $p < 0.05$ . All statistics were derived using the Statistical Package for the Social Sciences software package (SPSS, Chicago, IL).

## **CHAPTER IV**

### **MANUSCRIPT**

#### **Introduction**

The number of people living beyond a cancer diagnosis in the United States is expected to rise to almost 19 million by 2024 (NCI, 2016). Although cancer accounts for nearly one in four deaths, death rates are continuing to decline (NCI, 2016). Due to an increase in the number of cancer survivors (CS), cancer is being viewed as a chronic illness requiring long term management and rehabilitation (Spence et al., 2010). Cancer and its treatment can result in significant toxic side effects that impact the cardiopulmonary system. Cardiotoxicity from chemotherapy leads to decreases in cardiac output and aerobic capacity, resulting in complications such as cardiomyopathy and left ventricular dysfunction (Carver et al., 2007; Dy & Adjei, 2013; Eschenhagen et al., 2011; Yusuf et al., 2008;). Treatment toxicities can be amplified in elderly CS because gerontological populations are more inclined to have increased rates of heart failure, coronary artery disease, arrhythmias, and left ventricular dysfunction (Sawhney et al., 2005). Many cancer rehabilitation programs exist to combat the physiological deficits from treatment through exercise interventions and are primarily focused on improving quality of life.

Exercise interventions are feasible in CS and a prescriptive plan leads to physiological improvement in areas such as muscular strength and aerobic capacity

(Spence et al., 2010). Peak oxygen uptake ( $VO_{2peak}$ ) is a measure of aerobic fitness that is consistently lower in CS compared to age-matched healthy individuals, and is often directly affected by the cytotoxic therapies that adversely impact the organ systems involved in exercise (Jones et al., 2011). Exercise rehabilitation in CS has a positive impact on cardiorespiratory function and consequently increases  $VO_{2peak}$ . The results of a  $VO_{2peak}$  assessment can provide clinicians with baseline information needed to prescribe the correct intensity of exercise as well as the correct progression throughout a cancer rehabilitation program. Establishing valid assessment protocols that determine  $VO_{2peak}$  are essential for developing individualized exercise prescriptions for cancer rehabilitation programs.

Maximal cardiopulmonary exercise testing (CPET) is considered the gold standard for measuring  $VO_{2peak}$ , but it can be expensive, time consuming, and requires trained medical personnel to be present. CPET has been found to be safe and feasible for those with advanced cancer (Jones et al., 2007) but some CPET protocols may be too difficult for CS to complete while others provide inaccurate results (Shackelford et al., 2015). The University of Northern Colorado Cancer Rehabilitation Institute (UNCCRI) developed an accurate and valid treadmill protocol to estimate  $VO_{2peak}$  specifically for the cancer population. The UNCCRI treadmill protocol has decreased grades and speeds to accommodate virtually any pulmonary, musculoskeletal, and cardiovascular dysfunctions caused by cancer treatments (Shackelford et al., 2015). The UNCCRI treadmill protocol has more manageable increases in intensity and provides a useful  $VO_{2peak}$  value that allows for a complete and accurate exercise prescription (Shackelford et al., 2015).

The six-minute walk test (6MWT) is a submaximal exercise assessment used in many populations with chronic disease to predict  $VO_{2peak}$  (American Thoracic Society, 2002; Cahalin et al., 1996; Ross et al., 2010; Zugck et al., 2000), but it is not clear whether this test accurately assesses  $VO_{2peak}$  in CS. The 6MWT is favored in clinical populations because it is simple, inexpensive, and representative of activities of daily living. The purpose of this study was to evaluate the validity of the 6MWT for predicting  $VO_{2peak}$  compared to the UNCCRI treadmill protocol in CS.

## **Methods**

### **Subjects**

A total of 128 subjects participated in this study. All participants were CS enrolled in UNCCRI's cancer rehabilitation program. Participants were referred to UNCCRI and their medical records were provided by their oncologist or primary care physicians. Upon entering the program at UNCCRI, participants signed an informed consent approved by the University of Northern Colorado's Institutional Review Board agreeing to participate in research within the institute. From 2015-2016, participants entering the UNCCRI program enrolled in and completed this study. Existing clients already in the program were recruited via flyers within the clinic for participation. Participants were excluded if they had a history of congestive heart failure, myocardial infarction, chronic lung disease, asthma, significant ambulatory issues, history of coughing up blood, fainting, or epilepsy.

### **Experimental Design**

Participants who qualified for the study completed one UNCCRI treadmill protocol and one 6MWT one week apart in randomized order. Resting blood pressure

(BP), resting heart rate (RHR), blood oxygen saturation (SpO<sub>2</sub>), height (cm), and body weight (kg) were measured before each test. Blood pressure was measured manually by auscultation, HR was determined using a Polar® Heart Rate Monitor, SpO<sub>2</sub> was measured using a Clinical Guard® pulse oximeter, height was measured by the BSM170 stadiometer, and body weight was measured by the InBody 770®. Clinical Cancer Exercise Specialists (CES) ensured participant safety throughout both protocols. Five different VO<sub>2peak</sub> values were compared using a repeated measures ANOVA: 1) VO<sub>2peak</sub> obtained from the UNCCRI protocol, and 2) VO<sub>2peak</sub> values derived from four well-documented 6MWT prediction equations.

**University of Northern Colorado  
Cancer Rehabilitation Institute  
Treadmill Protocol**

There are 21 total stages of the UNCCRI treadmill protocol, each stage lasting one minute. Speed and/or grade was increased at the completion of each stage. Details of the protocol appear in Table 1. Participants were informed that they would be completing a UNCCRI Treadmill VO<sub>2peak</sub> protocol and could terminate the test at any time, but were encouraged to continue to their maximum effort.

Before each test, participants were given the following instructions: 1) BP will be taken every three minutes by a CES, 2) another CES will be recording HR and SpO<sub>2</sub> and changing speed and/or grade every minute, 3) a pulse oximeter will be placed on your finger for the duration of the test to monitor oxygen saturation every minute, 4) a CES will also stand behind you during the duration of the test for your safety and to ensure proper placement on the treadmill belt, 5) we ask that you push yourself to maximum exertion and although you may stop at any time, we would like you to reach the point



where you feel that you can't physically continue, 6) we recommend that you do not use the handrails unless you feel it is absolutely necessary, 7) you must choose to use or not use the handrails for the entire protocol, 8) after maximal exertion a cool down phase at a lower speed and grade will be initiated until vitals reach near-resting measures.

The test ended when the participant reached his or her perceived maximum exertion or could not continue further. The test concluded when the participant verbally expressed when they had reached their maximum rate of perceived exertion (RPE) using a modified Borg RPE, or when the participant physically grabbed onto the handrails to signal the end of the test. Once the participant indicated they had reached maximum effort, the cool down phase was initiated. When the participant's vitals were close to resting values and the participant indicated that they felt safe to get off the treadmill, the treadmill was stopped. Final vitals were recorded, including when the maximum HR was reached. The duration of the test until maximum exertion and the final completed stage were also recorded.

The American College of Sports Medicine (ACSM) running and walking equations were used to calculate  $VO_{2peak}$  from the last completed stage of the protocol. If the participant was walking at maximum exertion the following equation was used:

$$VO_{2peak} \text{ (mL/kg/min)} = (0.1 \times S) + (1.8 \times S \times G) + 3.5.$$

The variable S is the speed in meters/min and G is the percent grade in decimal form. If the participant was running at maximum exertion the following equation was used:  $VO_{2peak} = (0.2 \times S) + (0.9 \times S \times G) + 3.5$ . If the participant was using the handrails during the protocol the following equation was used:  $VO_{2peak} = 0.694 \times [\text{the ACSM walking/running value from above}] + 3.33$  (ACSM, 2013).

Table 2

*The University of Northern Colorado Cancer Rehabilitation Protocol*

| Stage      | Speed  | Grade | Time  |
|------------|--------|-------|-------|
| 0          | 1.0mph | 0%    | 1 min |
| 1          | 1.5mph | 0%    | 1 min |
| 2          | 2.0mph | 0%    | 1 min |
| 3          | 2.5mph | 0%    | 1 min |
| 4          | 2.5mph | 2%    | 1 min |
| 5          | 3.0mph | 2%    | 1 min |
| 6          | 3.3mph | 3%    | 1 min |
| 7          | 3.4mph | 4%    | 1 min |
| 8          | 3.5mph | 5%    | 1 min |
| 9          | 3.6mph | 6%    | 1 min |
| 10         | 3.7mph | 7%    | 1 min |
| 11         | 3.8mph | 8%    | 1 min |
| 12         | 3.9mph | 9%    | 1 min |
| 13         | 4.0mph | 10%   | 1 min |
| 14         | 4.1mph | 11%   | 1 min |
| 15         | 4.2mph | 12%   | 1 min |
| 16         | 4.3mph | 13%   | 1 min |
| 17         | 4.4mph | 14%   | 1 min |
| 18         | 4.5mph | 15%   | 1 min |
| 19         | 4.6mph | 16%   | 1 min |
| 20         | 4.7mph | 17%   | 1 min |
| Cool- Down | **     | 0%    | ***   |

### **The Six Minute Walk Test Protocol**

The 6MWT was conducted under the guidelines of the American Thoracic Society (ATS). The 6MWT took place in a 12.6-meter-long hallway at the UNCCRI. Prior to the 6MWT, participants performed a pulmonary assessment using a MIR Spirolab III® portable desktop spirometer to determine force vital capacity (FVC) and forced expiratory capacity (FEV<sub>1</sub>) of the lungs. Two CES's supervised the test to ensure participant safety.

At the beginning of the test each participant was given the following instructions: 1) walk up and down the hallway for six minutes, reaching the colored dot at each end of the hallway, 2) try to walk as far as possible in that six-minute time frame, and 3) at any time you can stop to rest or sit in one of the chairs, but we ask that you keep walking as soon as you feel able. The participants were asked to walk alone unless gait imbalances required them to have a CES near to assist them. At every minute, participants were told the time remaining and a standard verbal encouragement such as “Great job” was given. One CES kept track of the time on a stopwatch and placed a mark on the data collection sheet every time the participant completed one length of the hallway. At the end of the test, participants were asked to stop where they were and a CES marked on the wall where they had stopped. The CES measured the partial distance the participant had covered from the end of the hallway to the spot on the wall with a meter stick. This value was added to the total distance of lengths completed to ensure a precise measurement of the distance covered. At the end of the test HR, BP, RPE and SpO<sub>2</sub> values were recorded immediately by a CES.

The distance and variables such as age, height, weight, FVC and FEV<sub>1</sub> were used to calculate predicted VO<sub>2peak</sub> from four well established prediction equations: 1)  $VO_{2peak} = 0.03 \times \text{distance (m)} + 3.98$  (Cahalin et al., 1996), 2)  $VO_{2peak} = 0.02 \times \text{distance (m)} - 0.191 \times \text{age (yrs)} - 0.07 \times \text{weight (kg)} + 0.09 \times \text{height (cm)} + 0.26 \times (\text{RPP} \times 10^{-3}) + 2.45$  (Cahalin et al., 1996), 3)  $VO_{2peak} = 0.02 + \text{distance (m)} - 0.14 \times \text{age (yrs)} - 0.07 \times \text{weight (kg)} + 0.03 \times \text{height (cm)} + 0.23 \times (\text{RPP} \times 10^{-3}) + 0.10 \times \text{FEV}_1(\text{L}) - 1.19 \times \text{FVC (L)} + 7.77$  (Cahalin et al., 1996), and 4)  $VO_{2peak} = 4.948 + 0.023 \times \text{distance (m)}$  (Ross et al., 2010).

### **Statistical Analysis**

A power analysis was conducted using the statistical program G-power (Version 3.1) prior to the study to determine the appropriate sample size for significance. For both protocols a repeated measures ANOVA was utilized to examine the differences in VO<sub>2peak</sub> obtained by the UNCCRI treadmill protocol against the VO<sub>2peak</sub> values determined by the four 6MWT prediction equations. Paired t-tests were utilized to test the differences in HR and SBP between the UNCCRI protocol and the 6MWT protocol. A Pearson r-correlation between values obtained using the UNCCRI treadmill protocol and 6MWT equations 1-4 were run to determine the strength of the relationship in VO<sub>2peak</sub>. Significance was set to  $p < 0.05$ . All statistical analyses were conducted using the Statistical Package for the Social Sciences software package (SPSS, Chicago, IL).

## **Results**

### **Participant Characteristics**

Table 3 displays the cancer types, and Table 4 displays age, height, weight, and FVC/FEV<sub>1</sub> for study participants. Table 5 displays all resting characteristics for

participants prior to each test. The participants were comprised of 49 males and 79 females with a mean age of  $62 \pm 14$  years, a mean height of  $169 \pm 8$  cm, and a mean weight of  $78 \pm 20$  kg. Mean FVC was  $3.44 \pm 0.89$  L and mean FEV<sub>1</sub> was  $2.59 \pm 0.72$  L. Mean resting heart rate (RHR), systolic blood pressure (RSBP), and diastolic blood pressure (RDBP) before the UNCCRI treadmill test were  $82 \pm 14$  bpm,  $125 \pm 15$  mmHg and  $75 \pm 9$  mmHg, respectively. The mean RHR, RSBP, and RDBP before the 6MWT was  $78 \pm 14$  bpm,  $123 \pm 13$  mmHg and  $74 \pm 8$  mmHg, respectively. There was a significant difference observed between RHR before the treadmill and before the 6MWT ( $p = 0.003$ ). There was no significant difference observed in RSBP ( $p = 0.137$ ) and in RDPB ( $p = 0.419$ ) prior to each test. Twenty four percent of the CS were undergoing chemotherapy and/or radiation treatments during testing. All participants completed each of the VO<sub>2peak</sub> protocols without complications.

Table 3

| <i>Cancer Types</i> |    |
|---------------------|----|
| Cancer Type         | N  |
| Breast              | 51 |
| Prostate            | 19 |
| Lymphoma/Leukemia   | 12 |
| Colon               | 12 |
| Lung                | 7  |
| Skin                | 6  |
| Ovarian             | 5  |
| Renal               | 5  |
| Uterine             | 3  |
| Sarcoma             | 3  |
| Pancreatic          | 3  |
| Esophageal          | 2  |
| Multiple Myeloma    | 2  |
| Rectal              | 2  |
| Thyroid             | 1  |
| Ampullary           | 1  |
| Oropharyngeal       | 1  |
| Stomach             | 1  |
| Neuroendocrine      | 1  |

Table 4

| <i>Age, Weight, Height, FVC, FEV<sub>1</sub></i> |             |
|--|-------------|
| Age  | 62 ± 14     |
| Weight (kg)                                      | 78 ± 20     |
| Height (cm)                                      | 169 ± 8     |
| FVC (L)  | 3.44 ± 0.89 |
| FEV <sub>1</sub> (L)                             | 2.59 ± 0.72 |

Table 5

*Resting Characteristics*

|             | UNCCRI TM | 6MWT     | P-value |
|-------------|-----------|----------|---------|
| RHR (bpm)   | 82 ± 14   | 78 ± 14  | 0.003*  |
| RSBP (mmHg) | 125 ± 15  | 123 ± 13 | 0.137   |
| RDBP (mmHg) | 75 ± 9    | 74 ± 8   | 0.419   |

Note: RHR = resting heart rate; RSBP = resting systolic blood pressure; RDBP = resting diastolic blood pressure; \*denotes a p-value < 0.05.

Table 6

*Mean Peak Exercise Values*

|                     | UNCCRI TM  | 6MWT      | P-Value |
|---------------------|------------|-----------|---------|
| HR (bpm)            | 150 ± 21   | 109 ± 21  | <0.001* |
| SBP (mmHg)          | 150 ± 18   | 139 ± 20  | <0.001* |
| DBP (mmHg)          | 77 ± 10    | 75 ± 9    | 0.013*  |
| RPE                 | 9 ± 2      | 6 ± 2     | <0.001* |
| SO <sub>2</sub> (%) | 94 ± 3     | 95 ± 3    | <0.001* |
| TM Time (min)       | 10.5 ± 2.9 | -         | -       |
| Walk Distance (m)   | -          | 499 ± 101 | -       |

Note: HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; RPE = rate of perceived exertion; \*denotes significant differences between groups.

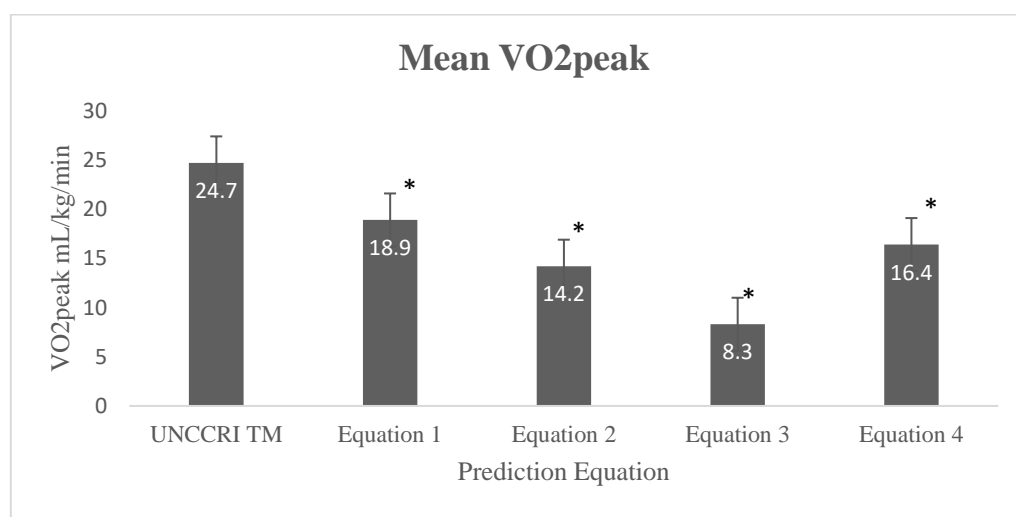
**Validity of Predicted VO<sub>2peak</sub> for the 6MWT**

Table 6 summarizes predicted peak oxygen consumption values of the UNCCRI treadmill test and the 6MWT. Average time spent on the treadmill was 10.5 ± 2.9 minutes and the average distance walked during the 6MWT was 499 ± 101 meters (m). 6MWT peak HR (109 ± 21 bpm), SBP (139 ± 20 mmHg), DPB (75 ± 9 mmHg), and RPE (6 ± 2) were significantly lower (p < 0.05) compared to the UNCCRI treadmill protocol peak HR (150 ± 21 bpm), SBP (150 ± 18 mmHg), DPB (77 ± 10 mmHg), and RPE (9 ± 2). Oxygen saturation during the 6MWT was significantly higher (95 ± 3) than

the UNCCRI protocol ( $94 \pm 3$ ) ( $p < 0.001$ ). The UNCCRI protocol yielded a significantly higher  $\text{VO}_{2\text{peak}}$  of  $24.7 \pm 7.4$  mL/kg/min compared to all four 6MWT prediction equations ( $p < 0.001$ ). Figure 1 displays the mean  $\text{VO}_{2\text{peak}}$  values for the UNCCRI treadmill protocol and all four 6MWT prediction equations. Equations 1, 2, 3 and 4 yielded  $\text{VO}_{2\text{peak}}$  values of  $18.9 \pm 3.0$ ,  $14.2 \pm 4.6$ ,  $8.3 \pm 3.8$ , and  $16.4 \pm 2.3$  mL/kg/min, respectively.

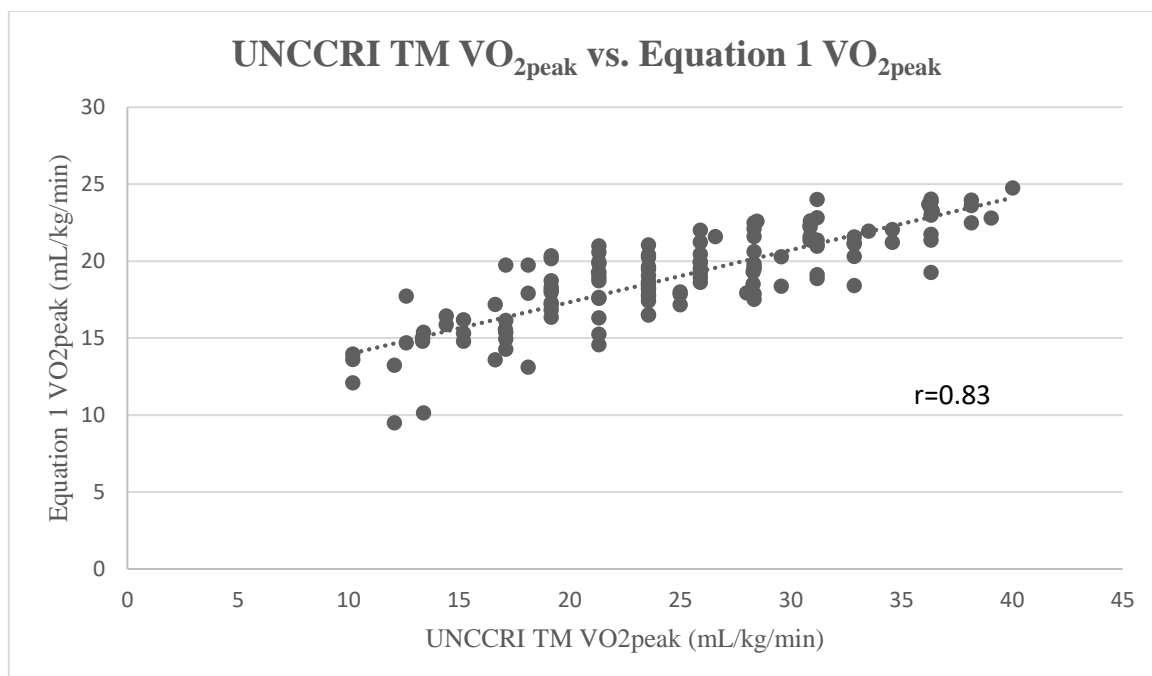
### Correlation Analyses

Figures 2-5 display correlations between the UNCCRI treadmill protocol and all four  $\text{VO}_{2\text{peak}}$  prediction equations. Positive strong correlations occurred between the UNCCRI treadmill protocol and 6MWT prediction equation 1 ( $r = 0.83$ ) and equation 4 ( $r = 0.83$ ). Moderately strong correlations occurred between the UNCCRI treadmill protocol and 6MWT equation 2 ( $r = 0.74$ ) and equation 3 ( $r = 0.70$ ).

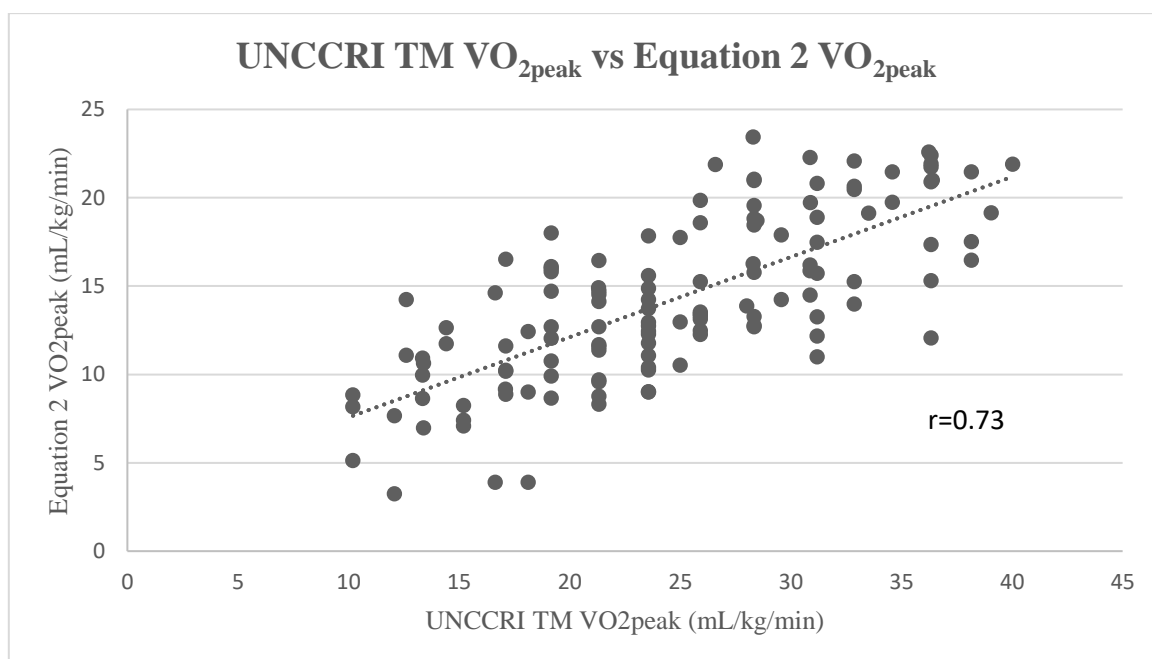


*Figure 1.* Mean  $\text{VO}_{2\text{peak}}$  values. \* denotes a significant difference ( $p < 0.001$ ) between the 6MWT prediction equation and the UNCCRI treadmill  $\text{VO}_{2\text{peak}}$  value.

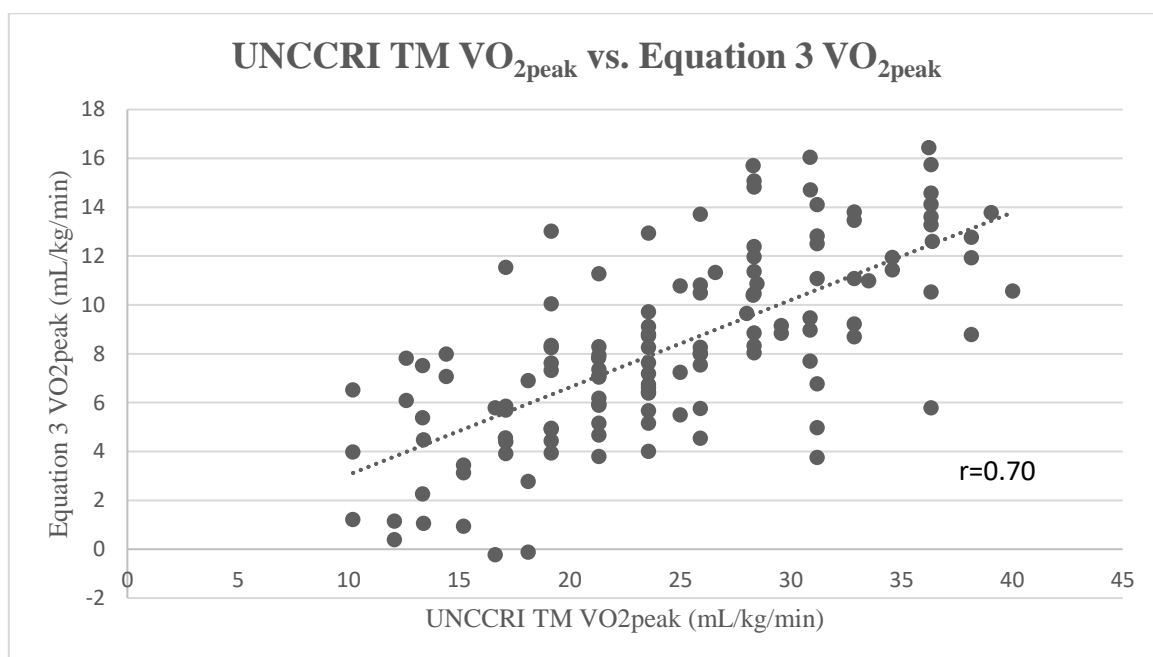




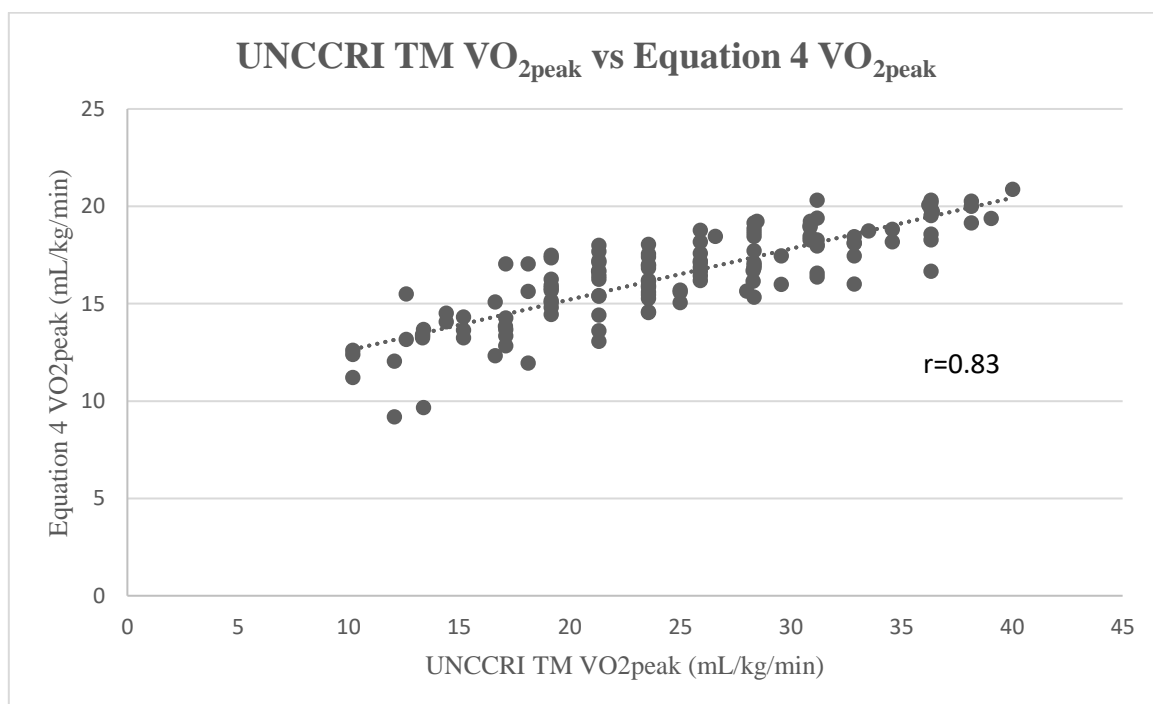
*Figure 2.* Correlation between UNCCRI Treadmill VO<sub>2peak</sub> and 6MWT prediction Equation 1 VO<sub>2peak</sub>.



*Figure 3.* Correlation between UNCCRI Treadmill VO<sub>2peak</sub> and 6MWT prediction Equation 2 VO<sub>2peak</sub>.



*Figure 4.* Correlation between UNCCRI Treadmill VO<sub>2peak</sub> and 6MWT prediction Equation 3 VO<sub>2peak</sub>.



*Figure 5.* Correlation between UNCCRI Treadmill VO<sub>2peak</sub> and 6MWT prediction Equation 4 VO<sub>2peak</sub>.

## Discussion

The aim of this study was to assess the validity of predicted  $\text{VO}_{2\text{peak}}$  from the 6MWT compared to the UNCCRI treadmill protocol in a cancer specific population. It was hypothesized that  $\text{VO}_{2\text{peak}}$  predicted from the 6MWT equations would be significantly lower than  $\text{VO}_{2\text{peak}}$  obtained from the UNCCRI treadmill protocol. This was confirmed with the UNCCRI protocol yielding significantly higher  $\text{VO}_{2\text{peak}}$  values ( $p < 0.001$ ) compared to all four 6MWT prediction values. Other studies have cautioned using 6MWT  $\text{VO}_{2\text{peak}}$  prediction equations in populations where individual monitoring is crucial due to the variability in  $\text{VO}_{2\text{peak}}$  values (Maldonado-Martin et al., 2006; Ross et al., 2010). Although Equation 1 was found to have a strong correlation with the UNCCRI protocol ( $r = 0.83$ ), the differences between  $\text{VO}_{2\text{peak}}$  values were significant ( $p < 0.001$ ), concluding that this trend isn't representative of validity. Maldonado-Martin et al. (2006) investigated Equation 1 and questioned the validity of using the walk test to determine functional capacity in elderly patients with heart failure (HF). In their study, the measured  $\text{VO}_{2\text{peak}}$  was  $13.5 \pm 2.9$  (mL/kg/min) while the prediction equation using 6MWT distance significantly overestimated  $\text{VO}_{2\text{peak}}$  ( $17.2 \pm 3.3$ ;  $p < 0.05$ ). The researchers concluded that predicting  $\text{VO}_{2\text{peak}}$  results in substantial variability and should not be used in HF patients where an accurate determination of functional capacity is essential. Ross et al. (2010) reviewed several studies and determined an equation to predict  $\text{VO}_{2\text{peak}}$  from 1083 patients with diverse cardiopulmonary disease diagnoses. Although a moderate correlation ( $r=0.59$ ) was found between distance covered and predicted  $\text{VO}_{2\text{peak}}$ , the standard estimation of error (SEE) was unacceptably large (3.82 mL/kg/min) for clinical usefulness in individual patients. They state that their prediction

equation, like other prediction equations, is of limited usefulness for individual patients. Like other disease populations, validity of functional capacity is imperative in CS.

Moderate to strong correlations were seen between the UNCCRI  $\text{VO}_{2\text{peak}}$  value and 6MWT  $\text{VO}_{2\text{peak}}$  values from Equation 1 ( $r = 0.83$ ) and Equation 3 ( $r = 0.70$ ). The correlations, although strong, do not validate the 6MWT because significant differences ( $p < 0.001$ ) were observed between the UNCCRI protocol and Equations 1-4. Several studies found similar positive correlations between  $\text{VO}_{2\text{peak}}$  measured during a CPET compared to  $\text{VO}_{2\text{peak}}$  during the 6MWT (Cahalin et al., 1996; Faggiano et al., 1997; Guazzi et al., 2009; Jehn et al., 2009; Zugck et al., 2000). In 37 patients with varying classifications of heart failure, a good positive correlation ( $r = 0.72$ ) was overall seen between the 6MWT  $\text{VO}_{2\text{peak}}$  and from a CPET  $\text{VO}_{2\text{peak}}$  (Jehn et al., 2009). However, when these patients were grouped according to their  $\text{VO}_{2\text{peak}}$ , the correlation was highly dependent on the functional impairment of the subjects. In subjects with a  $\text{VO}_{2\text{peak}}$  greater than 25.2 mL/kg/min, the 6MWT  $\text{VO}_{2\text{peak}}$  was significantly lower than the CPET test ( $23.4 \pm 2.6$  vs.  $27.6 \pm 3.3$ ). On the other hand, those with a  $\text{VO}_{2\text{peak}}$  equal to or lower than 17.5 mL/kg/min, the 6MWT  $\text{VO}_{2\text{peak}}$  was significantly higher than the CPET test ( $15.5 \pm 3.6$  vs.  $13.6 \pm 2.5$ ). It has been suggested that these data should be taken into careful consideration when using the 6MWT to evaluate clinical prognosis in patients with varying degrees of clinical disability (Jehn et al., 2009).

Other studies have reported similar results that at higher levels of functional capacity the 6MWT should not be used as a measure of  $\text{VO}_{2\text{peak}}$  (Deboeck et al., 2014; Fujino et al., 2015; Lipkin et al., 1986). Lipkin et al. (1986) found that maximal CPET tests may be more appropriate for patients who have mild HF, or a  $\text{VO}_2$  of greater than

20 mL/kg/min. On average, the CS in the current study had a  $\text{VO}_{2\text{peak}}$  over this threshold and it is concluded that a maximal CPET is more appropriate in CS. Even for the CS under this threshold, a maximum CPET was found to be more appropriate than the 6MWT. Deboeck et al. (2014) stated that a distance greater than 500m during the 6MWT results in the test becoming less sensitive to increases in  $\text{VO}_{2\text{peak}}$ . The average distance walked for our CS was 499m, which implies that one should be careful to interpret 6MWT  $\text{VO}_{2\text{peak}}$  as valid. Fujino et al. (2015) found a significant correlation in  $\text{VO}_{2\text{peak}}$  ( $r = 0.55$ ,  $p < 0.01$ ) for distances below 450m, but no correlation with distances greater than 450m ( $r = 0.304$ ,  $p = 0.193$ ). Several other studies report that there is not a significant correlation between the 6MWT  $\text{VO}_{2\text{peak}}$  and a CPET  $\text{VO}_{2\text{peak}}$  in healthy and elderly populations who have higher degrees of functional capacity compared to chronic disease populations (Deboeck et al., 2014; Green et al., 2001; Gremeaux et al., 2008). In healthy individuals, and those who may have early stage clinical disease or relatively high functional capacity, the 6MWT may not be suitable for evaluating exercise capacity (Jones, Eves, Haykowsky, Joy, & Douglas, 2008; Schmidt et al., 2013). The American Thoracic Society states that although investigators have used the 6MWT in clinical settings, this does not prove that the test is clinically useful or the best test for determining functional capacity (American Thoracic Society, 2002). The 6MWT itself can only estimate  $\text{VO}_{2\text{peak}}$ , and the information provided by the 6MWT should be considered complimentary to CPET but not a replacement for it.

All participants were able to safely complete both protocols with no significant adverse events. In CS, the 6MWT produced significantly lower heart rate values than the UNCCRI treadmill protocol ( $109 \pm 21$  bpm vs.  $150 \pm 21$  bpm, respectively). This

supports the conclusion that the 6MWT in a cancer specific population is a submaximal protocol and should not be used to assess  $\text{VO}_{2\text{peak}}$ . Other studies have demonstrated similar results with significant differences in heart rate values between the walk test and a CPET test for several disease and healthy populations (Blanco et al., 2010; Cavalheri et al., 2016; Deboeck et al., 2014; Green et al., 2001; Gremeaux et al., 2008; Zugck et al., 2000). Contrary to these results, other researchers found that the walk test elicited a maximal exercise response in participants with a low  $\text{VO}_{2\text{peak}}$ , questioning the test as a submaximal protocol in other disease populations (Faggiano et al., 1997; Jehn et al., 2009). Faggiano et al. (1997) found the walk test to be questionable as a submaximal test in HF populations because 73% of subjects were above anaerobic threshold at termination. Lower HR values during the 6MWT are likely seen because the participant sets their own pace. It was uncommon to find CS putting in maximum effort, even when the stated goal of the test is to walk as far as possible in that time frame. This was also demonstrated by the results of the RPE for participants. For the UNCCRI treadmill protocol the RPE averaged  $9 \pm 2$  and the walk test only averaged  $6 \pm 2$  on a scale of 0-10. The treadmill requires participants to undergo increased intensities until they reach their maximum effort, while the 6MWT is purely subjective. The test is self-paced and motivation is a large factor that can account for up to 30% of the variability (Enright, 2003). Although some CS may prefer a submaximal test because of treatment-related side effects, a treadmill protocol may be necessary to help factor out motivation levels. The significant difference seen between RHR before the treadmill and before the walk test is likely due to the CS being apprehensive about a treadmill test.

It was hypothesized that the multivariate prediction equations taking into account individual differences in height, weight and other physiologic variables would have a higher correlation with the UNCCRI treadmill protocol. The correlation found between Equation 3 and the UNCCRI protocol was actually lower ( $r = 0.70$ ) compared to Equation 1 and the UNCCRI protocol ( $r = 0.83$ ). Equation 3 had a lower correlation with the UNCCRI protocol most likely due to this equation being derived from a cardiac, not cancer specific, population. These results demonstrate that these specific equations cannot be used to accurately assess  $VO_{2peak}$  in a cancer specific population.

### **Limitations and Future Directions**

There were several limitations to this study. First, the hallway distance at the UNCCRI was only 12.6 meters and a longer hallway may have increased final distance due to the participants not having to turn around as often (Beekman et al., 2013). However, course length has been shown to not significantly affect the results of the 6MWT with courses greater than 15 meters (Sciurba et al., 2003; Weiss, 2000). Second, gas analysis was not utilized in either test to confirm  $VO_{2peak}$  results, although the UNCCRI protocol has been validated in a prior study using gas analysis ( $r = 0.93$ ) (Shackelford et al., 2015). Third, CS already enrolled at the UNCCRI have previously undergone UNCCRI treadmill assessments and the familiarity with the protocol compared to the 6MWT could allow them to perform at a higher level. Last, motivation levels could have been affected by the CES assisting with the protocols if the participant was already enrolled at the UNCCRI and had been familiar with them and their training style. For future research, a longer track and gas analysis during both protocols might be suggested to strengthen statistical significance and validity. Future studies might also

provide the necessary data for equations to be developed that could more accurately assess  $VO_{2peak}$  from the 6MWT in CS. Although a small portion of this study, those participants who utilized the handrails during the treadmill protocol had less significant differences in  $VO_{2peak}$  during the treadmill and 6MWT prediction Equation 1. This trend should be further investigated to see if the 6MWT is more accurate in CS who have to utilize the handrails during a treadmill assessment.

### **Conclusion**

This study assessed the validity of predicting  $VO_{2peak}$  from the 6MWT compared to the UNCCRI treadmill protocol in a cancer specific population. Findings suggest that the 6MWT is not a valid test for predicting  $VO_{2peak}$  in CS due to the fact that all four 6MWT prediction equations significantly underestimated  $VO_{2peak}$  in CS. Our results demonstrate that CS can safely complete maximal protocols for the best  $VO_{2peak}$  value. Other studies have concluded that cancer survivors can safely complete peak cardiopulmonary exercise testing (De Backer et al., 2007; Jones et al., 2007; Kilka et al., 2009; May et al., 2010). Even those CS with limited functional capacity who needed to utilize the handrails could do so with accurate results. The 6MWT may be favored because of the limited exercise capacity often seen in CS, but shouldn't be substituted as an assessment tool in CS for  $VO_{2peak}$ . The completion of a maximal assessment provides more precise results that lead to more accurate prescription intensities to progress exercise capacity safely over the course of rehabilitation. It is proposed that cancer rehabilitation clinics do not use the 6MWT to evaluate  $VO_{2peak}$ , and to instead use the UNCCRI treadmill protocol to obtain  $VO_{2peak}$ .



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**APPENDIX A**

**INFORMED CONSENT FOR PARTICIPATION  
IN RESEARCH**

**INFORMED CONSENT**

[FOR PARTICIPATION IN RESEARCH AT UNCCRI]

UNIVERSITY OF  
**NORTHERN  
COLORADO****Cancer  
Rehabilitation  
Institute**

NAME \_\_\_\_\_

DATE \_\_\_\_\_

**PROJECT TITLE : Exercise Interventions to Attenuate the Negative Side-Effects of Cancer Treatments**

University of Northern Colorado Cancer Rehabilitation Institute

Reid Hayward, Ph.D., Director  
 Phone Number: 970-351-1821  
 reid.hayward@unco.edu

Jessica Brown, Ph.D., Clinical Coordinator  
 Phone Number: 970-351-1724  
 jessica.brown@unco.edu

The University of Northern Colorado Cancer Rehabilitation Institute (UNCCRI) and the School of Sport and Exercise Science support the practice of protection of human subjects participating in research. The following information is provided for you to decide whether you wish to participate in either the standard UNCCRI program or if recruited, specific research investigations. You should be aware that even if you agree to participate, you are free to withdraw at any time without affecting opportunities for participation in other programs offered by this department.

This program is involved with the assessment of your body composition, pulmonary function, cardiovascular endurance, muscular strength and endurance, range of motion and flexibility. Skinfold calipers will be used to measure body composition (body fat percentage). The pulmonary function test will be measured through maximum exhalation into a sterile mouthpiece. Measuring oxygen consumption on a motor-driven treadmill will assess your cardiorespiratory capacity. Assessment of muscular strength and endurance will occur through the use of weights, dumbbells, a handgrip dynamometer, and other established tests. Flexibility and range of motion will be measured by the modified sit-and-reach test and the reaching test. Baseline measurements such as: heart rate, blood pressure, height, weight, and circumference measurements will be taken for risk stratification and safety during your participation. Forms to be completed for the program include cancer history, medical history, lifestyle/activity questionnaire, and psychological tests such as depression scales, quality of life, fatigue and cognitive functioning. Blood may be drawn with your permission at various time points during your participation. Once all of the tests are completed, the results will be analyzed and an exercise prescription will be written. You may then have the option of participating in a three month exercise intervention based on your testing results. The expected benefits associated with your participation in this program include information regarding your level of physical fitness and recommended fitness and lifestyle changes necessary to improve your quality of life and health.

Page 1 of 2  
 Please Initial \_\_\_\_\_

If you are recruited, and agree to participate in a specific research investigation, additional exercise, psychological, and/or cognitive tests may be administered. Your optional three month exercise intervention may also differ, but the expected benefits should still include improved quality of life and health. All participants at UNCCRI will be under the direction of the UNCCRI Director and Clinical Coordinator but other persons will be associated or assist with the data collection. Your participation is solicited, although strictly voluntary. The obtained data may be used in reports or publications but your identity will not be associated with such reports. We at UNCCRI take mental distress that may accompany health issues seriously and will attempt to support you with counseling referrals and information on local cancer support groups if this is an issue. Our staff is required to report evidence of clear and imminent danger.

This research should not result in physical injury, however, some soreness may occur and some of the fitness tests can be uncomfortable. Additionally, with the blood draws you may feel temporary discomfort. The duration of the discomfort is short. Please give your consent with full knowledge of the nature and purpose of the procedures, the benefits that you may expect, and the discomforts and/or risks which may be encountered. We appreciate your assistance.

Participation is voluntary. You may decide not to participate in this study and if you begin participation, you may still decide to stop and withdraw at any time. Your decision will be respected and will not result in loss of benefits to which you are otherwise entitled. Having read the above and having had an opportunity to ask any questions, please sign below if you would like to participate in this research. A copy of this form will be given to you to retain for future reference if requested. If you have any concerns about your selection or treatment as a research participant, please contact Sherry May, IRB Administrator, Office of Sponsored Programs, Kepner Hall, University of Northern Colorado Greeley, CO 80639; 970-351-1910.

\_\_\_\_\_  
Signature of Subject Agreeing to Participate

By signing this consent you certify you are at least 18 years of age.

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Researcher

\_\_\_\_\_  
Date

**APPENDIX B**  
**INSTITUTIONAL REVIEW BOARD**  
**APPROVAL**



*Institutional Review Board*

DATE: March 28, 2016

TO: Reid Hayward, PhD  
FROM: University of Northern Colorado (UNCO) IRB

PROJECT TITLE: [573297-4] Exercise Interventions to Attenuate the Negative Side-Effects of Cancer Treatments

SUBMISSION TYPE: Continuing Review/Progress Report

ACTION: APPROVED

APPROVAL DATE: March 26, 2016

EXPIRATION DATE: March 26, 2017

REVIEW TYPE: Expedited Review

Thank you for your submission of Continuing Review/Progress Report materials for this project. The University of Northern Colorado (UNCO) IRB has APPROVED your submission. All research must be conducted in accordance with this approved submission.

This submission has received Expedited Review based on applicable federal regulations.

Please remember that informed consent is a process beginning with a description of the project and insurance of participant understanding. Informed consent must continue throughout the project via a dialogue between the researcher and research participant. Federal regulations require that each participant receives a copy of the consent document.

Please note that any revision to previously approved materials must be approved by this committee prior to initiation. Please use the appropriate revision forms for this procedure.

All UNANTICIPATED PROBLEMS involving risks to subjects or others and SERIOUS and UNEXPECTED adverse events must be reported promptly to this office.

All NON-COMPLIANCE issues or COMPLAINTS regarding this project must be reported promptly to this office.

Based on the risks, this project requires continuing review by this committee on an annual basis. Please use the appropriate forms for this procedure. Your documentation for continuing review must be received with sufficient time for review and continued approval before the expiration date of March 26, 2017.

Please note that all research records must be retained for a minimum of three years after the completion of the project.

If you have any questions, please contact Sherry May at 970-351-1910 or [Sherry.May@unco.edu](mailto:Sherry.May@unco.edu). Please include your project title and reference number in all correspondence with this committee.

**APPENDIX C**


**UNIVERSITY OF NORTHERN COLORADO  
CANCER REHABILITATION INSTITUTE  
TREADMILL PROTOCOL**

Client Name: \_\_\_\_\_  
Date: \_\_\_\_\_

Client ID #: \_\_\_\_\_

*Prior to testing take resting HR, BP, and Weight*

Date of Birth: \_\_\_\_\_ Age: \_\_\_\_\_ Phase: \_\_\_\_\_ RHR: \_\_\_\_\_ RBP: \_\_\_\_\_  
Est. HR Max: \_\_\_\_\_

Body Weight (lbs): \_\_\_\_\_  Kg (lbs/2.2): \_\_\_\_\_ Is this the same data acquired from an initial assessment/reassessment? Y N

### RMCRI Cancer Treadmill Protocol Worksheet

| Stage     | Speed  | Grade | Time  | BP | HR | RPE | SpO <sub>2</sub> |
|-----------|--------|-------|-------|----|----|-----|------------------|
| 0         | 1.0mph | 0%    | 1 min |    |    |     |                  |
| 1         | 1.5mph | 0%    | *     |    |    |     |                  |
| 2         | 2.0mph | 0%    | *     |    |    |     |                  |
| 3         | 2.5mph | 0%    | *     |    |    |     |                  |
| 4         | 2.5mph | 2%    | *     |    |    |     |                  |
| 5         | 3.0mph | 2%    | *     |    |    |     |                  |
| 6         | 3.3mph | 3%    | *     |    |    |     |                  |
| 7         | 3.4mph | 4%    | *     |    |    |     |                  |
| 8         | 3.5mph | 5%    | *     |    |    |     |                  |
| 9         | 3.6mph | 6%    | *     |    |    |     |                  |
| 10        | 3.7mph | 7%    | *     |    |    |     |                  |
| 11        | 3.8mph | 8%    | *     |    |    |     |                  |
| 12        | 3.9mph | 9%    | *     |    |    |     |                  |
| 13        | 4.0mph | 10%   | *     |    |    |     |                  |
| 14        | 4.1mph | 11%   | *     |    |    |     |                  |
| 15        | 4.2mph | 12%   | *     |    |    |     |                  |
| 16        | 4.3mph | 13%   | *     |    |    |     |                  |
| 17        | 4.4mph | 14%   | *     |    |    |     |                  |
| 18        | 4.5mph | 15%   | *     |    |    |     |                  |
| 19        | 4.6mph | 16%   | *     |    |    |     |                  |
| 20        | 4.7mph | 17%   | *     |    |    |     |                  |
| Cool-Down | **     | 0%    | *     |    |    |     |                  |

\*Identify time for each the final stage and for the cool-down.  
 \*\*Identify speed for cool-down.

Note: **If client changes from a walk to a run during this test, identify the time when the gait changed.**

Was the client holding the handrails?    Yes    No

Was the client running during the last stage completed?    Yes    No    If Yes,  
 what time did running start: \_\_\_\_\_

VO<sub>2</sub> Peak (L/Min) : \_\_\_\_\_    VO<sub>2</sub> Peak (mL/kg/min) : \_\_\_\_\_

Peak RER: \_\_\_\_\_    Max HR: \_\_\_\_\_

FINAL TIME to peak/volitional fatigue: \_\_\_\_\_ as a decimal  
 (minutes . (sec/60)) \_\_\_\_\_



**APPENDIX D**

**SIX MINUTE WALK TEST PROTOCOL**

## Six Minute Walk Test Data Collection

Client Name: \_\_\_\_\_ Client ID #: \_\_\_\_\_ Date: \_\_\_\_\_

Date of Birth: \_\_\_\_\_ Age: \_\_\_\_\_ Phase: \_\_\_\_\_

RHR: \_\_\_\_\_ RPB: \_\_\_\_\_ Est. HR Max: \_\_\_\_\_

Body Weight (lbs): \_\_\_\_\_ Body Weight (kg): \_\_\_\_\_ Height (ft., in.) \_\_\_\_\_

FEV<sub>1</sub> (L): \_\_\_\_\_ FVC (L): \_\_\_\_\_ Height (cm): \_\_\_\_\_

**Equipment needed for test:** ☐ two stethoscopes ☐ two BP cuffs ☐ pulse ox ☐ HR monitor

☐ sticky notes ☐ measuring stick ☐ two portable chairs ☐ stopwatch ☐

|  |  |
|--|--|
| Place a mark for every length of the hallway completed |  |
|--|--|

Total number of hall lengths walked: \_\_\_\_\_

Partial length distance: \_\_\_\_\_ (ft, in.)

### After Completion of the Test:

HR: \_\_\_\_\_ BP: \_\_\_\_\_ RPE: \_\_\_\_\_ SPO<sub>2</sub> \_\_\_\_\_

**Conversions:**      **1in = 2.54 cm**      **12 in = 1 foot**      **1m = 100cm**  
**1 meter = 3.28 feet**      **39.37 inches = 1 meter**      **RPP= SBP x HR**

**Hallway Distance: 1 length = 12.6 meters**

Total Lengths Walked: \_\_\_\_\_ \* 12.6 = \_\_\_\_\_ meters

Partial Length Distance: \_\_\_\_\_ (ft, in.) = \_\_\_\_\_ inches = \_\_\_\_\_ meters

Total Distance Walked (m) = (# of lengths\*12.6m) + partial distance (m)

\_\_\_\_\_ total lengths walked (m) + \_\_\_\_\_ partial distance (m) =

**Total Distance Walked (m) = \_\_\_\_\_**

***Cahalin Equation 1:***

**Peak VO<sub>2</sub> = 0.03 x distance (m) + 3.98**

Peak VO<sub>2</sub> = 0.03 x \_\_\_\_\_ (m) + 3.98

Peak VO<sub>2</sub> (mL/kg/min): \_\_\_\_\_

***Cahalin Equation 2:***

**Peak VO<sub>2</sub> = 0.02 x distance(m) - 0.191 x age(yr) - 0.07 x weight(kg) + 0.09 x height(cm) + 0.26 x RPP x 10<sup>-3</sup> + 2.45**

Peak VO<sub>2</sub> = 0.02 x \_\_\_\_\_ (m) - 0.191 x \_\_\_\_\_ (yr) - 0.07 x \_\_\_\_\_ (kg) + 0.09 x \_\_\_\_\_ (cm) + 0.26 x \_\_\_\_\_ (RPP) x 10<sup>-3</sup> + 2.45

Peak VO<sub>2</sub> (mL/kg/min): \_\_\_\_\_

***Cahalin Equation 3:***

**Peak VO<sub>2</sub> = 0.02 x distance(m) - 0.14 x age(yr) - 0.07 x weight(kg) + 0.03 x height(cm) + 0.23 x RPP x 10<sup>-3</sup> + 0.10 x FEV<sub>1</sub> (L) - 1.19 x FVC (L) + 7.77**

Peak VO<sub>2</sub> = 0.02 x \_\_\_\_\_ (m) - 0.14 x \_\_\_\_\_ (yr) - 0.07 x \_\_\_\_\_ (kg) + 0.03 x \_\_\_\_\_ (cm) + 0.23 x \_\_\_\_\_ (RPP) x 10<sup>-3</sup> + 0.10 x \_\_\_\_\_ (L) - 1.19 x \_\_\_\_\_ (L) + 7.77

Peak VO<sub>2</sub> (mL/kg/min): \_\_\_\_\_

***Ross Equation:***

**Mean Peak VO<sub>2</sub> = 4.948 + 0.023 \* mean 6MWD (meters)**

Mean Peak VO<sub>2</sub> = 4.948 + 0.023 \* \_\_\_\_\_ (m)

Peak VO<sub>2</sub> (mL/kg/min): \_\_\_\_\_

**APPENDIX E**  
**ABBREVIATIONS**

ACSM – American College of Sports Medicine  
ATS – American Thoracic Society  
BP – Blood Pressure  
CAD – Coronary Artery Disease  
CES – Cancer Exercise Specialist  
COPD – Chronic Obstructive Pulmonary Disease  
CPET – Cardiopulmonary Exercise Testing  
CRF – Cardiorespiratory Fitness  
CS – Cancer Survivor  
DBP – Diastolic Blood Pressure  
FEV1 – Forced Expiratory Capacity  
FVC – Forced Vital Capacity  
HF – Heart Failure  
HR – Heart Rate  
NCSLC – Non-small Cell Lung Cancer  
RDBP – Resting Diastolic Blood Pressure  
RER – Respiratory Exchange Ratio  
RHR – Resting Heart Rate  
RPE – Rate of Perceived Exertion  
RPP – Rate Pressure Product  
RSBP – Resting Systolic Blood Pressure  
SBP – Systolic Blood Pressure  
SEE – Standard Error of Estimation  
SPO<sub>2</sub> – Blood Oxygen Saturation  
UNCCRI – University of Northern Colorado Cancer Rehabilitation Institute  
US – United States  
VO<sub>2max</sub> – Maximum Volume of Oxygen Consumption  
VO<sub>2peak</sub> – Peak Volume of Oxygen Consumption  
6MWT – Six Minute Walk Test